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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,883	12/21/2000	Hans-Ulrich Demuth	20784-5	1277

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 07/21/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/745,883	DEMUTH ET AL.	
	Examin r	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5-8,14 and 16* is/are ~~allowed.~~ free of art

6)☒ Claim(s) *4,9-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-16 are pending.

Applicants' amendment filed April 28, 2003 (Paper No. 21) is acknowledged. Applicants' response has been fully considered. Claims 1, 4, 7-9, 11 and 14 have been amended, and a new claim 16 has been added. Thus, claims 1-16 are examined.

Oath/Declaration

2. A substituted oath/declaration filed January 13, 2003 is acknowledged. However, the oath or declaration is still defective because non-initialed and/or non-dated alterations have been made to the address of the inventor, Peter Jorn Schmidt. See 37 CFR 1.52(c).

Information Disclosure Statement

3. Most references listed in the information Disclosure Statement (IDS) filed April 28, 2003 (paper No. 22) have been considered. However, the references without English translation are not considered.

Objection Withdrawn

4. The previous objection to claims 8, 9, 11 and 14 is withdrawn in view of the amendment to the claim, and applicants' response at page 6 in Paper No. 21.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

5. The previous rejection of claims 1-15, under 35 U.S.C.112, second paragraph, regarding the term " derivative", or lacking antecedent base regarding "dipeptide cyanide", is withdrawn in

view of applicants' amendment to the claims, and applicants' response at pages 8-9 in Paper No. 21.

Claim Rejections - 35 USC § 102

6. The previous rejection of claims 1, 8-12 and 15, under 35 U.S.C.102 (b) as being anticipated by Bachovchin *et al.* (WO 93/08259) is withdrawn in view of applicants' amendment to the claims, and applicants' response at page 10 in Paper No. 21.

7. The previous rejection of claims 1-3, 5 and 7-11, under 35 U.S.C.102 (b) as being anticipated by Bachovchin *et al.* (WO 95/11689) is withdrawn in view of applicants' amendment to the claims, and applicants' response at page 10 in Paper No. 21.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 9-13 and 15 are directed to a method of preparing a pharmaceutical composition for temporally controlled in vivo enzymatic inhibition of DP IV comprising a compound of A-B-C and a pharmaceutical carrier (claims 9 and 10); and a method of treating metabolic disorders such as diabetes mellitus and impaired glucose tolerance in mammals that can be treated by modulating the DP IV enzymatic activity of a mammal, comprising administering

the compound A-B-C, where C is an unstable inhibitor of DP IV containing a dipeptide having a C-terminus active carbonyl group, wherein the unstable inhibitor does not contain a boronate, phosphonate or trifluoroalkyl ketone group (claims 11-13 and 15). The specification, however, only discloses cursory conclusions (page 3, lines 15-17; page 5, lines 7-14) without data supporting the findings, which state that the compounds of unstable inhibitors of DP IV can be used for the treatment of disorders in mammals by modulating the DP IV enzymatic activity, especially metabolic disorders associated with diabetes mellitus. There are no indicia that the present application enables the claimed methods in view of treating a metabolic disorder in mammals as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the claimed methods are enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the treating conditions for various metabolic disorders using the claimed compounds, and the effects of the compounds in the treatment, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the claimed methods in association with various metabolic disorders in mammals.

(3). The state of the prior art and relative skill of those in the art:

The specification indicates the prior art (e.g., DE 19616486) has shown how modulation of DP IV activity with DP IV inhibitors (e.g., Ile-thiazolidide) influences various diseases states such as metabolic disorders (page 2, lines 7-10), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the treatment of various metabolic disorders in mammals with the claimed compounds to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of preparing a pharmaceutical composition for temporally controlled in vivo enzymatic inhibition of DP IV comprising a compound of A-B-C and a pharmaceutical carrier ; and a method of treating metabolic disorders such as diabetes mellitus in mammals by modulating the DP IV enzymatic activity, comprising administering the compound A-B-C, where C is an unstable inhibitor of DP IV containing a dipeptide having a C-terminus active carbonyl group. The specification indicates the compounds containing the unstable inhibitors of DP IV can be used for treating various metabolic disorders, especially disorders associated with diabetes mellitus, and the masked inhibitor is more effective than the non-masked inhibitors because the masked compound produces a marked improvement in glucose tolerance in Wistar rats (page 3, lines 15-21). However, the specification has not demonstrated the use of any compound containing unstable DP IV inhibitor in treating any

metabolic disorder, or any disease associated with diabetes mellitus, nor has indicated how to prepare a pharmaceutical composition comprising the compound for in vivo inhibiting DP IV. There is no disclosure indicating the treating conditions such as the dose and the effect of the compound, nor demonstrating the end point of the treatment using the claimed compound. Moreover, there are no working examples indicating the use and the effect of the compound in treating various metabolic disorders. Since the specification fails to provide sufficient guidance on the preparation of the pharmaceutical composition comprising the compound, and the treating conditions of various metabolic disorders, one skilled in the art would not know how to treat the diseases, thus, it is necessary to have additional guidance/teachings and to carry out further experimentation to assess the effects of the compounds.

(5). Predictability or unpredictability of the art:

The claim encompasses using a compound comprising an unstable inhibitor of DP IV to treat various metabolic disorders in mammals, since the treating conditions for various disorders are not sufficiently described, the outcome of the claimed invention is highly unpredictable.

(6). Nature of the Invention

The claim are directed to treating various metabolic disorders associated with DP IV enzymatic activity using a compound comprising an unstable inhibitor of DP IV, however the specification has not demonstrated the treatment of these metabolic disorders. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example is lacking, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have

additional guidance and to carry out further experimentation to assess the effect of the compound in treating various metabolic disorders related to DP IV enzymatic activity.

In response, applicants indicate "the written description" only requires applicants to provide an enabling description of the invention to one of ordinary skill in the art, it does not require demonstrating the use of a compound, and the applicants must merely provide sufficient details to allow one skilled in the art to practice the invention; the claims are limited to those metabolic disorders that will respond to a modulation in enzymatic activity of DP IV, for example, the prior art (DE 19616486) discloses using DP IV inhibitors, it is possible to prevent or alleviate metabolic anomalies such as diabetic mellitus; Applicants claim a method of treating metabolic disorders that can be treated by modulating the DP IV enzymatic activity by administering an effective amount of a compound with a formula A-B-C; and the specification has provided the method of administration, dosing and the effect of the compound (see pages 5, 8, 9 of the specification; pages 6-8 of the response). The comments in the response have been assessed in view of the current enablement rejection. The argument is not found persuasive because the specification only indicates the amount of the inhibitor for inhibiting DP IV in vivo is different in individual cases, and the compound in the pharmaceutical composition can be used for treatment of metabolic disorders by modulating the DP IV activity, the specification does not provide sufficient guidance and teachings on treating conditions such as effective dose used for treating metabolic disorders, nor indicates the effect of the inhibitor in the treatment, as indicated in the section above, without such guidance and teachings, one skilled in the art would not know how to practice the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 4, 11-13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 4 is indefinite because of the use of the terms "Thia" and "Pyr", it is not clear what the term means. A full chemical name should be indicated in the first occurrence.

In response, applicants "Thia" denotes "thiazolidine" and "Pyr" denotes pyrrolidine, and these denotations are commonly accepted by the one skilled in the art (page 9 of the response). The argument is not found persuasive because it is not clear what the term indicates without its full chemical name.

11. Claims 11-13 and 15 are indefinite because they lack essential steps as claimed in the method of treating disorders. The omitted step is the outcome for the treatment. Claims 12, 13 and 15 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. Claims 11, 12 and 15 are also indefinite as to "metabolic disorders", it is not clear what metabolic disorder is intended.

In response, applicants indicate claim 11 has been amended to cite "a therapeutically effective amount of the compound", and the specification has disclosed each organism will release the exact amount of inhibitor that is necessary to inhibit the amount of DP IV that is present, which is different in individual cases (page 9 of the response). The argument is not fully persuasive because the claim only cites administration of "a therapeutically effective amount of

the compound" but without recitation of the endpoint of the treatment, thus it is not clear what the effective amount of the compound would do.

Conclusion

12. Claims 4, 9-13 and 15 are rejected, it appears claims 1-3, 5-8, 14 and 16 are free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

Christopher S. Low

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July 16, 2003